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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,981	06/27/2001	Roland Gerritsen van der Hoop	01722906	3783

7590 10/16/2003

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EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	15

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/892,981	Applicant(s) VAN DER HOOP, ROLAND GERRITSEN	
	Examiner San-ming Hui	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7-29,45,47 and 51-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 7-29, 45, 47, and 51-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments filed July 25, 2003 have been entered.

Claims 1, 3, 7-29, 45, 47, and 51-73 are pending.

The outstanding rejection under 35 USC 112, second paragraph is withdrawn in view of the amendments filed July 25, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 7-13, 20-27, 45, 47, 51-57, and 64-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubin (US Patent 5,5059,603), Ebert et al. (US Patent 5,152,997), and AndroGel Monograph from IDS received December 9, 2002 in view of Langtry et al. (Drugs 1999; 57(6): 967-989), Leucuta et al. (abstract of Clujul

Medical, 1983 ;56(4) :371-376), and Rheology Modifiers Handbook, 2000, page 81-88, published by William Andrew Publishing.

Rubin teaches methyl testosterone is useful in a method of treating androgen deficiency associated disorders such as impotence (See particularly col. 2, line 59 - col. 3, line 11).

Ebert et al. teaches testosterone therapy is a useful in a method of treating male hypogonadism and the conditions associated male hypogonadism comprising employing a matrix containing testosterone and penetration enhancer onto the skin (See col. 1, line 20-66).

AndroGel monograph teaches a testosterone hydroalcoholic gel useful to treat male hypogonadism (See Indication and Usage Section). AndroGel monograph teaches the hydroalcoholic gel comprises ethanol and isopropyl myristate (See the Description Section).

The references do not expressly teach the dosage form of the instant invention to be a gel comprising polyacrylic acid as thickening agent. The references do not expressly teach the method of treating menopause disorder, such as erectile dysfunction, by employing the combination of testosterone as a topical gel and methyltestosterone an oral dosage form, optionally with addition of sildenafil. The references do not expressly the dosage of methyltestosterone to be 0.2 mg to about 50.0mg and that of testosterone to be 0.1g to about 100.0g. The references do not teach the employment of sildenafil in the method herein.

Langtry et al. teaches that sildenafil is useful to treat erectile dysfunction (See abstract).

Leucuta et al. teaches methyltestosterone may be formulated to oral tablet with increasing bioavailability proportionally to dosage (see abstract).

Rheology Modifiers Handbook teaches that polyacrylic acid is a well known pharmaceutical aid as thickening agent (See page 81, page 82, page 83-84, Table 2.2a, Pharmaceutical Grades Section).

It would have been obvious to one skill in the art when the invention was made to employ the combination of testosterone as a topical gel and methyltestosterone as an oral dosage form, optionally with addition of sildenafil in a method of treating menopausal disorders in a mammal. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate polyacrylic acid as thickening agent in the hydroalcoholic gel. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed dosage in the herein claimed method.

One of ordinary skill in the art would have been motivated to employ the combination of testosterone and methyltestosterone, optionally with addition of sildenafil in a method of treating menopausal disorders in a mammal because testosterone, and methyltestosterone are all known in the art to be useful in method of treating both male menopausal disorders. Employing two of these agents which are known to be useful to treat male menopausal disorders individually into a single method useful for the very same purpose is *prima facie* obvious, absent evidence to the contrary. See *In re*

Kerkhoven 205 USPQ 1069. Such composition would have been reasonably expected to be useful in treating erectile dysfunction secondary to male menopausal disorder. Further incorporation of sildenafil, which is known to treat erectile dysfunction, with the male menopausal treating steroid composition would also be reasonably expected as beneficial and effective in treating erectile dysfunction. At least additive effect would be expected.

Furthermore, one of ordinary skill in the art would have been motivated to incorporate polyacrylic acid as thickening agent in the hydroalcoholic gel since polyacrylic acid is a well known thickening agent. Incorporating any well known excipient into the gel formulation would be obvious as being within the purview of skilled artisan, absent showing the criticality of using such old and well known thickening agent. Moreover, the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary.

Claims 1, 3, 15-23, 28-29, 45, 47, 58-67, and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Place (US Patent 6,117,446) in view Remington's Pharmaceutical Sciences (1990, 18th ed., pages 1305 and 1314), Merck Index (11th ed., 1989, page 821, monograph 5103), Leucuta et al. (abstract of Clujul Medical, 1983 ;56(4) :371-376), and Rheology Modifiers Handbook, 2000, page 81-88, published by William Andrew Publishing.

Place teaches a method of hormonal replacement therapy and symptoms thereof such as female sexual dysfunction and vaginal dryness comprising a treatment of a woman with an estrogen such as estradiol and an androgenic steroid such as testosterone and methyltestosterone (See col. 7, line 35; col. 11, line 6-61). Place also teaches that the dosage of the estradiol may be 0.05 to 0.5 mg (See col. 11, line 36-61). Place also teaches that the dosage of the androgenic agent such as testosterone to be 0.1 to 2.5mg (See col. 11, line 44-45). Place also teaches that the estradiol and/or testosterone can be formulated in dosage form such as lozenges and tablets (See col. 12, line 29).

The reference does not expressly teach the dosage form of the instant invention to be a gel comprising isopropyl myristate, ethanol, and polyacrylic acid. The reference does not expressly teach the method of treating menopause disorder by employing the combination of estradiol as a topical gel and methyltestosterone as an oral dosage form. The reference does not expressly the dosage of methyltestosterone to be 0.2 mg to about 50.0mg and that of estradiol to be 0.1g to about 100.0g.

Remington's Pharmaceutical Sciences teaches that ethanol is a commonly used pharmaceutical solvent (See page 1314-1315).

Merck Index teaches that Isopropyl myristate is useful in topical pharmaceutical preparation where good penetration through skin is desired (See page 821, col. 1).

Leucuta et al. teaches methyltestosterone may be formulated to oral tablet with increasing bioavailability proportionally to dosage (see abstract).

Rheology Modifiers Handbook teaches that polyacrylic acid is a well known pharmaceutical aid as thickening agent (See page 81, page 82, page 83-84, Table 2.2a, Pharmaceutical Grades Section).

It would have been obvious to one skill in the art when the invention was made to incorporate ethanol, polyacrylic acid, and Isopropyl myristate as the excipients in the gel formulation herein. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ estradiol, as a topical gel and methyltestosterone, as an oral dosage form, in the herein claimed dosage, to treat female menopausal disorders in a mammal.

One of ordinary skill in the art would have been motivated to incorporate ethanol, polyacrylic acid, and Isopropyl myristate as the excipients in the gel formulation herein since ethanol, polyacrylic acid, and Isopropyl myristate are well known excipient for formulating gel. Incorporating any well known excipient into the gel formulation, including ethanol, polyacrylic acid, and Isopropyl myristate, would be obvious as being within the purview of skilled artisan, absent showing the criticality of using such old and well known.

One of ordinary skill in the art would have been motivated to employ estradiol, as a topical gel and methyltestosterone, as an oral dosage form, in the herein claimed dosage, to treat female menopausal disorders in a mammal because estradiol and methyltestosterone are known to be useful, in combination, to treat female menopausal disorders such as vaginal dryness. Administering these two agents in the herein claimed dosage form is considered obvious as being within the purview of skilled

artisan. The skilled of artisan would possess all conventional administration method of the active compounds such as oral and topical administration. The selection of one or another route of administration would be seen as a simple selection from among obvious alternatives.

Response to Arguments

Applicant's rebuttal arguments filed July 25, 2003 averring Rubin's teaching away have been considered but are not found persuasive. Rubin is merely teaching the side effects of methyltestosterone. Examiner notes that every drug would have certain side effects. The mere recitation of adverse effect of the medication cannot be served as teaching away. When taking the cited prior art together, as a whole, administering different hormonal agents together would be reasonably expected to reduce the dose of methyltestosterone, and therefore, would minimize the adverse effect of methyltestosterone thereby.

Applicant's rebuttal arguments filed July 25, 2003 averring Ebert's teaching away have been considered but are not found persuasive. Ebert simply states the problem that the invention therein has overcome. Therefore, it is seen that Ebert is not teaching away from delivering testosterone transdermally.

Applicant's rebuttal arguments filed July 25, 2003 averring the cited prior art's failure to provide motivation of employing the herein claimed agents concomitantly in the herein claimed method have been considered, but are not found persuasive. Since testosterone, and methyltestosterone are all known in the art to be useful in method of treating both male menopausal disorders, employing two of these agents into

a single method useful for the very same purpose is *prima facie* obvious, absent evidence to the contrary (See *In re Kerkhoven* 205 USPQ 1069).

Applicant's rebuttal arguments filed July 25, 2003 averring the cited prior art's failure to suggest the employment of methyltestosterone and estradiol in the herein claimed dosage forms and dosages have been considered, but are not found persuasive. Examiner notes that one of ordinary skill artisan would be charged to have the knowledge to formulate various conventional dosage forms of the well-known substances such as estradiol and methyltestosterone. Furthermore, the optimization of result effect parameters (e.g., dosage range, dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary. Such evidence is not seen herein.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

THEODORE J. CRIARES
PRIMARY EXAMINER
GROUP 1200/700

San-ming Hui
Patent Examiner
Art Unit 1617